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Zimmer Phocomelia: Delineation by Principal Coordinate Analysis

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We present a 46,XX stillborn fetus with tetraphocomelia, absence of ears, severe hypoplasia of nose, cleft palate, pulmonary hypoplasia, imperforate anus and vagina, and phallus-like structure on an otherwise undefined perineum. The pattern of abnormalities resembles the tetraphocomelic condition described by Zimmer et al. in 1985. Tetraphocomelia, ear/nose hypoplasia with facial clefts, pulmonary hypoplasia, and defects of the caudal end including imperforate anus, and abnormal genitalia constitute a distinct pattern of malformation termed Zimmer phocomelia. Principal coordinate analysis with Gower's similarity index supported the clinical impression that cases reported by Zimmer and the present case are distinct from other phocomelic conditions.

Although Zimmer phocomelia is currently referred to as "X-linked amelia," documentation of a female case with a penis-like structure in this report as well as consanguinity in the original family in Zimmer's report indicates that this condition is likely inherited in an autosomal recessive fashion. Zimmer phocomelia may be a more appropriate name than X-linked amelia.

KEY WORDS: X-linked amelia, principal coordinate analysis, numerical taxonomy, absent ears, ambiguous genitalia

INTRODUCTION

In 1985 Zimmer et al. described seven purportedly male infants in an inbred Arab kindred with tetraphocomelia, pulmonary hypoplasia, and facial clefts [Zimmer et al., 1985; Gershoni-Baruch et al., 1990]. Rodríguez et al. reported a similar case with severe involvement of the caudal axis [1992]. Several cases with tetraphocomelia and similar anomalies have been reported [Rosenak et al. 1991; Zlotogora et al., 1993; Baçaran et al.,1994; Mollica et al., 1995]. However, the relationship between these cases has been unclear.

We report on a stillborn, 46,XX fetus with a pattern of malformation comparable to that described by Zimmer et al. Clinical review and principal coordinate analysis of the tetraphocomelic conditions listed above define Zimmer phocomelia as a malformation pattern distinct from other types of phocomelia.

The presence of an XX karyotype in the present case plus the high degree of consanguinity in the family reported by Zimmer et al. suggest that this pattern of malformation may have an autosomal recessive mode of inheritance rather than an X-linked one.

CLINICAL REPORT

A macerated stillborn fetus was delivered at 32 weeks of gestation to a 32-year-old G3P2 Hispanic woman who did not receive prenatal care until shortly before delivery when she experienced vaginal bleeding. An ultrasound examination showed fetal death and oligohydramnios. The fetus had severe tetraphocomelia (Fig. 1). The weight of 521 g was <3rd centile for 32 weeks. Head circumference measured 23.3 cm with a crown rump length of 20.2 cm. There were four rudimentary limbs, each of which was approximately 4 cm long. Four fingers were present on each hand. The toes were absent. No distinct elbow, wrist, knee, or ankle joints were identified. The fetus had severe craniofacial malformations. No frontal bone or supra-orbital ridge could be palpated. No external ear or canal was present. The palpebral fissures measured 0.5 cm. The nose was rudimentary with two patent nares. The mouth was small. A V-shaped cleft of the palate was present. The external genitalia were malformed. There was a phallus-like structure that measured 1 cm on an otherwise undefined perineum without evidence of scrotal folds, perineal raphé, or labia. The anus was imperforate. Sex was not assignable from appearance.

Radiographs documented the following (Fig. 2): tetraphocomelia: each upper limb consisted of a U-shaped humerus combined with an abnormal articulation to a forearm bone; the hands consisted of four

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Fig. 1. Tetra-phocomelic 46,XX, fetus. Note the absence of external ear and rudimentary nose.

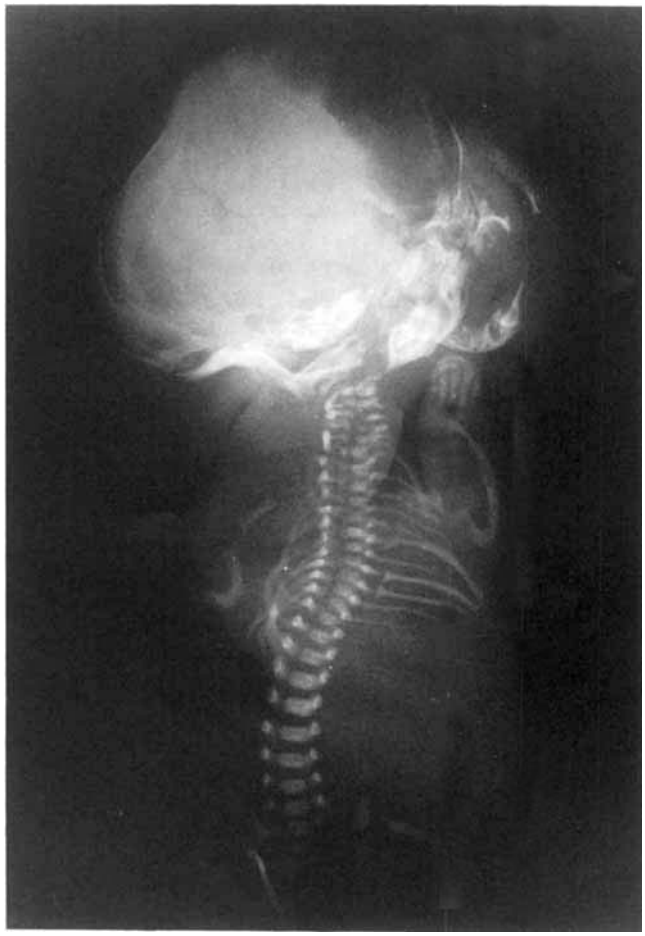

Fig. 2. X-ray film of the fetus. Note the cranial bone defect and rudimentary scapula and pelvis.

metacarpals with hypoplastic phalanges; each lower limb consisted of a single L-shaped bone. The feet were small with four metatarsal bones without phalanges or other tarsal bones. Calcification in the scapula and pelvis was rudimentary. Frontal bones were absent.

Autopsy demonstrated bilateral pulmonary hypoplasia with congenital adenomatoid malformation; lungs were monolobated. The total lung weight was 0.5 g as opposed to 15 g expected for total body weight. The larynx was hypoplastic with minimal cartilage; the trachea was patent but also hypoplastic. The mainstem bronchi were not identified. Sections of lungs showed abnormal arrangement of fibrous tissue, vessels, cartilage, and respiratory epithelium including cyst formation. Cartilage was seen only in the right lung. The kidneys were diffusely dysplastic. Sections showed dense connective tissue with large vessels, cystic spaces, primitive ducts surrounded by rings of fibrous tissue and only rare poorly formed glomeruli. Histologic sections of the genital tubercle showed a small urethralike structure. There were no vagina, uterus, or ovaries. The colon ended in a dilated pouch in the left lower quadrant. In addition, there was probable absence of the gallbladder, thyroid gland, and spleen. Ectopic thymus was present in the right thoracic cavity. The brain was autolyzed. Tissue culture of the placenta demonstrated 46,XX karyotype. Premature centromere separation in C-banding study was not present. The parents were not consanguineous and had a normal boy and girl.

DISCUSSION

This patient has many traits seen in the tetraphocomelic condition described by Zimmer et al. and designated "X-linked phocomelia" elsewhere [Zimmer, 1985; Gershoni-Baruch, 1990] including tetraphocomelia, absence of ears, severe hypoplasia of nose, facial cleft, pulmonary hypoplasia, imperforate anus and vagina, and abnormal genitalia.

This type of phocomelia may be distinguished on clinical grounds from the two other well-described phocomelia syndromes: Roberts-SC phocomelia and DK phocomelia. It is separated from classic Roberts-SC phocomelia by severe craniofacial involvement, severe genital malformations, and pulmonary hypoplasia. In addition, premature centromere separation, which is seen in 79% of patients with Roberts syndrome [Van Den Berg and Francke, 1993], has not been demonstrated in the one patient of Zimmer's in whom a study was performed, nor was it documented in the present case. One unusual case of Roberts syndrome with premature centromere separation was reported by Mann et al. [1982]. The infant had some signs of

Zimmer phocomelia including facial cleft, "dysplastic" ears, genital abnormality, kidney agenesis, and pulmonary hypoplasia. DK phocomelia, although associated with ear, kidney, and pulmonary abnormalities, is characterized by encephalocele and relatively intact lower limbs [Urioste et al., 1994; Lubinsky et al., 1994].

A number of other authors have described cases of phocomelia with traits which overlap those seen in the subject of this report and Zimmer's original family; however, classification of these cases has remained problematic. The isolated case reported by Rodríguez et al. with tetra-amelia, oblique facial cleft, absent ears, malformed nose, pulmonary hypoplasia, anencephaly, and severe caudal dysgenesis including imperforate anus and hypoplastic penis shows striking similarity to the Zimmer's as well as the present case [1992].

Al-Awadi/Raas-Rothschild syndrome is represented by tetraphocomelia, severe pelvic hypoplasia, and genital abnormalities [Al-Awadi et al., 1985; Camera et al., 1992; Raas-Rothschild et al., 1988]. Although this pattern of organ involvement is partially similar to that of the present case and Zimmer's case, the face is usually spared and severity of the external genital defects, such as anterior displacement is milder in Al-Awadi/Raas-Rothschild syndrome. However, Molica et al. recently reported a female infant who shared considerable similarity with Al-Awadi/Raas-Rothschild syndrome in that she had tetraphocomelia with pelvic bone hypoplasia along with absence of external genitalia [1995]. In addition she had bilateral cleft lip and palate and anteriorly displaced anus. Mollica et al. argued that this could represent a more severe form of Al-Awadi/Raas-Rothschild syndome. It is equally possible that this patient had a milder form of Zimmer phocomelia.

Schinzel phocomelia, which was suggested to be same as Al-Awadi/Raas-Rothschild syndrome by Lurie and Wulfsberg [1993], typically presents with defects of the lower limbs and pelvic bones, and is sometimes associated with defects of the cranial bones and genitalia [Schinzel, 1990]. However, those patients usually have normal facial structure and relatively intact upper limbs without pulmonary hypoplasia.

A combination of amelia, lung hypoplasia/aplasia, and cleft lip/palate has been found to be a distinct entity that is transmitted in an autosomal recessive fashion in four families of Muslim Arab ancestry [Baçaran et al., 1994; Rosenak, et al., 1991; Zlotogora et al., 1993]. Although these patients have amelia, pulmonary hypoplasia, and facial cleft, we argue that this condition is distinct from Zimmer's because none of them had anal atresia, pelvic hypoplasia, and absence of ears or nose.

In order to better define the phenotypic relationships between the pattern of malformation in the case herein described and that seen in Zimmer's family, DK phocomelia, Al-Awadi/Raas-Rothschild syndrome, Schinzel phocomelia, and the various unclassified cases, we have used the numerical taxonomy which was initially applied to dysmorphogenesis by Preus [Preus and Rex, 1983; Aymé and Preus 1984; Preus et al., 1985] and reintroduced by Verloes [1995]. Principal coordinate analysis is a technique for providing a geometrical representation of "distances" between individuals in multidimensional space (that is, how unlike each of N individuals of a sample is in relation to each other assessed on p variables; "individuals" corresponds to each of phocomelic conditions and "variable" to phenotypic sever-

TABLE I. Tabulated Data for the Principal Coordinate Analysis*

	Present case	Zimmer	Rodríguez	Mollica	Al-Awadi	Raas-Rothschild
Facial cleft	1	1	1	1	0	0
Ear	2	2	1	1	0	0
Nose	1	2	2	0	0	0
Neural tube defects	0	0	1	0	0	1
Cranial bone	1	0	1	0	0	0
Anus	2	2	2	1	0	0
External genitalia	2	1	2	2	1	1
Kidney	1	0	1	0	0	1
Pulmonary hypoplasia	1	1	1	0	0	0

	Camera	Schinzel phocomelia	Rosenak	Baçaran	DK phocomelia	Roberts syndrome
Facial cleft	0	0	1	1	0	1
Ear	1	0	0	0	1	1
Nose	0	0	0	0	0	1
Neural tube defects	0	1	0	0	1	1
Cranial bone	1	1	0	0	1	1
Anus	0	0	0	0	2	0
External genitalia	1	1	0	1	1	1
Kidney	0	0	0	0	2	1.5
Pulmonary hypoplasia	0	0	1	1	1	1

* Facial cleft (1 = present); ear (2 = absent; 1 = dysplastic); nose (2 = absent; 1 = hypoplastic); neural tube defects (1 = present); cranial bone defect (1 = present); anus (2 = imperforate; 1 = anteriorly displaced); external genitalia (2 = absent; 1 = dysplastic); kidney (1 = absent and 0.5 = dysplastic for each kidney); lung (2 = aplasia; 1 = hypoplasia). Score of 0 was given when particular characteristic was normal.

ity score of each phenotype). In this model each phenotypic character is coded using a binary or graded rating system following Verloes' convention [1995]. For external characters, the presence of anomalies was sought in the text and tables. When the written description was lacking, it was estimated whenever possible from the illustrations. For obvious qualitative abnormalities for which the authors were silent (clefts etc.), we hypothesized that in full length papers, missing information meant a normal trait. Absence of visceral anomalies was assumed only when a autopsy or pertinent radiologic evaluations were performed. We have chosen nine signs of severity which were scored as indicated in Table I. Finally, familial cases were combined to give a highest score in each phenotypic category. Table I summarizes the severity score on nine characteristics among 12 phocomelic conditions.

The principal coordinate analysis was performed obtaining Gower's similarity index (see Appendix). The result of the principal coordinate analysis is depicted in three-dimensional space in Figure 3. The present case is located very close to the family reported by Zimmer and the patient reported by Rodríguez. Cases reported by Al-Awadi, Raas-Rothschild, and Schinzel phocomelia are rather close to each other and seem to form a distinct group. The case reported by Camera is located close to this group. Cases reported by Baçaran and Rosenak constitute another distinctive cluster. DK phocomelia, the case reported by Mollica et al., and the atypical case of Roberts syndrome reported by Mann do not form distinctive clusters and remain problematic.

Principal coordinate analysis supports that Zimmer's original family, the case herein reported, and the case of Rodríguez et al. constitute a pattern that is distinct from other phocomelia syndromes. The description herein of an XX affected individual supports an autosomal rather than X-linked mode of inheritance. The original familial condition described by Zimmer et al. has been presumed to be X-linked recessive and has been referred to as X-linked amelia because of the marked pre-

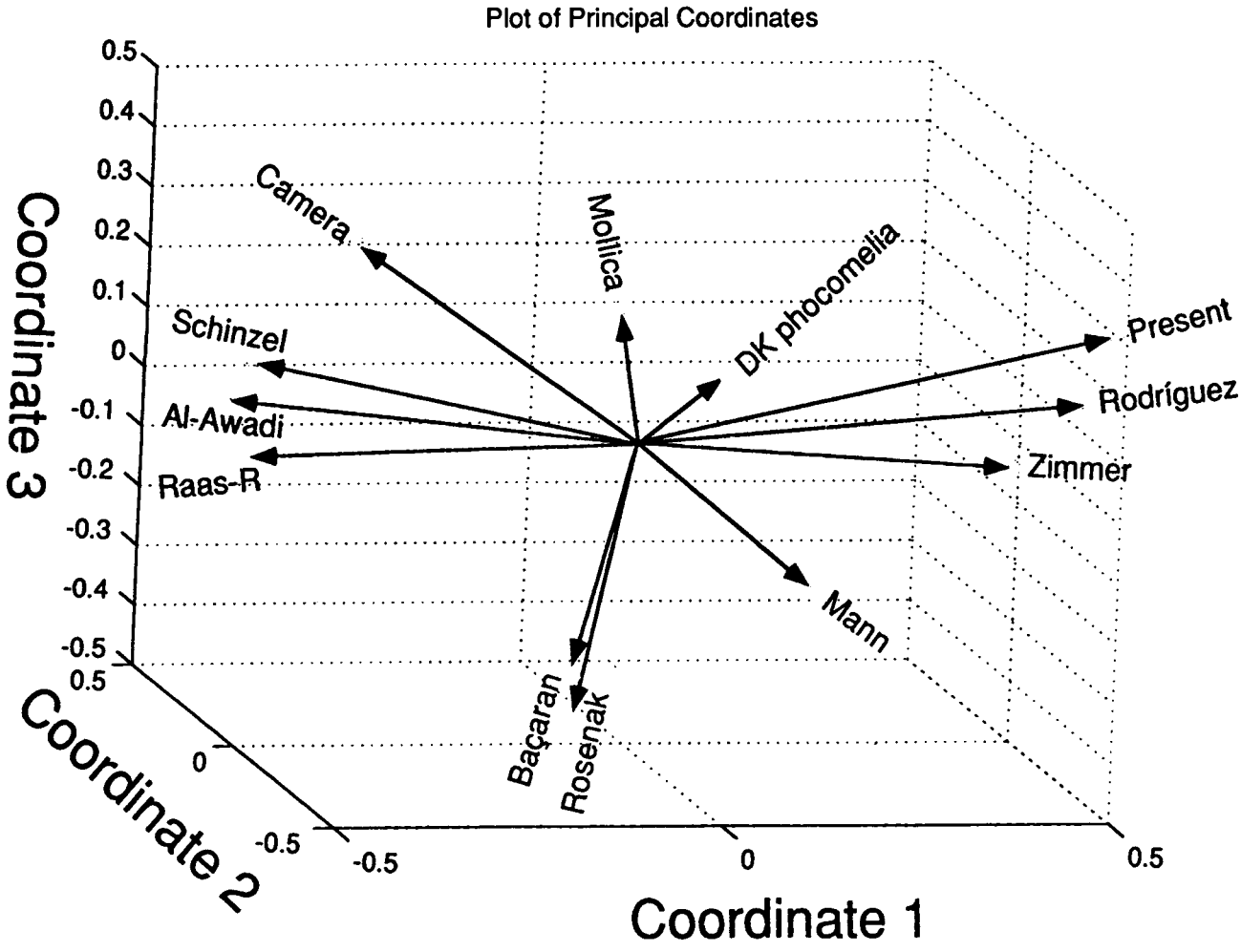

Fig. 3. Principal coordinate analysis of phocomelic conditions. Each condition is plotted according to its first, second, and third principal coordinate values. Closeness of two conditions in this coordinate indicates similarity between them.

dominance of "males." However, male sex assignment either by karyotyping or pathologic examination was done only in one of seven cases. Considering the rudimentary genitalia observed in the present case, male sex could have easily been presumed because of the phallic structure. Therefore it is possible that at least some of the individuals who were designated as males in the literature, had an 46,XX karyotype. This possibility in conjunction with consanguinity in the original family [Zimmer et al., 1985; Gershoni-Baruch et al., 1990] supports the contention that this condition may be an autosomal recessive disorder. We propose that this condition be called "Zimmer phocomelia" instead of "X-linked amelia" based on these considerations.

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APPENDIX

Principal coordinate analysis is a technique for providing a geometrical representation of "distances" between individuals. We employed the methodology defined by Gower transforming the original data matrix (shown in Table I) [1966, 1971]. Three latent roots of the 12×12 association matrix were extracted. The latent vectors were scaled so that the sum of the squares of the each element of each vector equals the corresponding root. Most of the distance information is contained in the first three latent roots. In Figure 3 are plotted 13 phocomelic conditions according to their first, second, and third principal coordinates. All computations were performed with "princrd1" program by Marcus [available from anonymous ftp at life.bio.sunysb.edu in the directory, /pub/morphmet] with the Student Edition of MATLAB v4 for Macintosh (Prentice Hall, Englewood Cliffs, NJ).